WEST Search History

DATE: Wednesday, July 10, 2002

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DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L13	l9 and l12	4	L13
L12	water soluble with polymer	61895	L12
L11	l9 and l10	0	L11
L10	water soluble near polymer	32431	L10
L9	l6 and L8	23	L9
L8	l7 and surfactant	102286	L8
L7	polymer	1375819	L7
L6	l5 and l4	33	L6
L5	l2 and l3	107	L5
L4	particle	1033494	L4
L3	solution or dissolv$3 or dissolution or solubili$6	1969390	L3
L2	cilostazol	129	L2
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L1	cilostazol	105	L1

END OF SEARCH HISTORY

L13: Entry 3 of 4 File: USPT Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117455 A
TITLE: Sustained-release microcapsule of amorphous water-soluble pharmaceutical active agent

Abstract Paragraph Left (1):
A sustained-release microcapsule contains an amorphous water-soluble pharmaceutical agent having a particle size of from 1 nm-10 .mu.m and a polymer. The microcapsule is produced by dispersing, in an aqueous phase, a dispersion of from 0.001-90% (w/w) of an amorphous water-soluble pharmaceutical agent in a solution of a polymer having a wt. avg. molecular weight of 2,000-800,000 in an organic solvent to prepare an s/o/w emulsion and subjecting the emulsion to in-water drying.

Brief Summary Paragraph Right (2):
JP-A 57-118512 discloses a process for producing sustained-release microcapsules of a water-soluble drug which comprises encapsulating the drug by coacervation phase separation. This process has the following disadvantages: (1) the water-soluble drug is leaked out to the outer aqueous phase, and the drug entrapment ratio decreases, and it is difficult to obtain microcapsules having a high drug content, and (2) the resulting microcapsules have many pores and cause a large initial drug release. Journal of Pharmaceutical Science Vol. 75, No. 8, p. 750-755 (1986) discloses a process for producing microspheres which comprises preparing an s/o/w type emulsion from a dispersion of micronized dry powder of cisplatin in a poly(dl-lactide) solution and subjecting the emulsion to an in-water drying process. However, this literature fails to teach or suggest amorphous cisplatin or sustained-release of the drug over a long period.

Brief Summary Paragraph Right (6):
The present inventors have intensively studied to achieve the above objectives. As a result, it has been found that a microcapsule comprising an amorphous water-soluble physiologically active substance and a polymer has a high entrapment of the physiologically active substance and causes a small initial release of the physiologically active substance. After further studies based on this finding, the present invention has been accomplished.

Brief Summary Paragraph Right (7):
The present invention provides a microcapsule comprising an amorphous water-soluble physiologically active substance and a polymer.

Brief Summary Paragraph Right (8):
The present invention also provides a microcapsule which is obtainable by dispersing in an aqueous phase a dispersion of an amorphous water-soluble physiologically active substance in a solution of a polymer in an organic solvent to prepare an s/o/w type emulsion and subjecting the emulsion to in-water drying.

Brief Summary Paragraph Right (9):
The present invention also provides a process for producing a microcapsule, which comprises dispersing in an aqueous phase a dispersion of an amorphous water-soluble physiologically active substance in a solution of a polymer in an organic solvent to prepare an s/o/w type emulsion and subjecting the emulsion to in-water drying.

Detailed Description Paragraph Right (5):
The amorphous physiologically active substance used in the present invention is soluble in water. The term "soluble in water" or "water-soluble" means that the water-solubility of the physiologically active substance is generally not less than

about 1 g, preferably not less than about 3 g, more preferably not less than about 5 g, per 100 ml of water at 20.degree. C. Preferably, the physiologically active substance is readily soluble in water. The term "readily soluble in water" means that the water-solubility of the physiologically active substance is not less than about 5 g, preferably not less than about 10 g, per 100 ml of water at 20.degree. C.

Detailed Description Paragraph Right (23):
Examples of the anti-platelet aggregation agents include ticlopidine, cilostazol, alprostadil, limaprost, dipyridamole, ethyl icosapentaenoate, beraprost, ozagrel, aspirin, etc.

Detailed Description Paragraph Right (46):
The amount of the water-soluble physiologically active substance to be used varies with factors related to the particular kind of physiologically active substance, desired pharmacological activity, duration time, etc. The concentration of the physiologically active substance in the solution of a polymer in an organic solvent is about 0.001 to 90% (W/W), preferably about 0.01 to 80% (w/W), more preferably about 0.01% to 70% (w/w).

Detailed Description Paragraph Right (47):
The physiologically active substance is preferably used in the form of microparticles. The average particle size of the physiologically active substance is generally about 1 nm to about 10 .mu.m, preferably about 1 nm to about 1 .mu.m.

Detailed Description Paragraph Right (48):
The polymer to be used in the present invention is a slightly water-soluble or water-insoluble polymer having biocompatibility. Examples of the polymers include biodegradable polymers such as poly fatty acid esters (e.g., polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, polylactic acid caprolactone, etc.), poly-.alpha.-cyanoacrylic acid esters, poly-.beta.-hydroxybutyric acid, polyalkylene oxalates (e.g., polytrimethylene oxalate, polytetramethylene oxalate, etc.), poly ortho esters, poly ortho carbonates and other polycarbonates (e.g., polyethylene carbonate, polyethylene-propylene carbonate, etc.), polyamino acids (e.g., poly-.gamma.-benzyl-L-glutamic acid, poly-L-alanine, poly-.gamma.-methyl-L-glutamic acid, etc.), hyaluronic acid esters, etc. Other biocompatible copolymers include polystyrene, polymethacrylic acid, copolymer of acrylic acid and methacrylic acid, polyamino acids, dextran stearate, ethylcellulose, acetylcellulose, nitrocellulose, maleic anhydride copolymers, ethylene-vinylacetate copolymer, polyvinylacetate, polyacrylamide, etc.

Detailed Description Paragraph Right (49):
These polymers may be used alone or in combination thereof. They may be used in the form of a copolymer or a mixture of these two or more polymers. They may also be in the form of salts thereof.

Detailed Description Paragraph Right (50):
Among these polymers, biodegradable polymers are particularly preferred for injections. In the case of lactic acid/glycolic acid copolymer (PLGA), for example, the biodegradability (i.e., degradability in living bodies) is defined as the percentage (w/w) of water-soluble low-molecular weight fragments degraded from PLGA based on PLGA and it should be more than 10% in one year after subcutaneous or intramuscular administration, preferably more than 80% in three months after subcutaneous or intramuscular administration. The biodegradable polymer is preferably a polyester. Preferred examples of the biodegradable polymers include polymers or copolymers of hydroxycarboxylic acids or mixtures thereof.

Detailed Description Paragraph Right (55):
The polymer to be used in the present invention can be synthesized by general synthetic methods as, for example, disclosed in JP-A 61-28521 without any problems.

Detailed Description Paragraph Right (56):
In general, the weight-average molecular weight of the polymer to be used in the present invention is preferably about 2,000 to about 800,000, more preferably about 5,000 to about 200,000.

Detailed Description Paragraph Right (57):
When lactic acid/glycolic acid copolymer is used as the above polymer, the molar ratio of lactic acid/glycolic acid is preferably 100/0 to 25/75, more preferably 100/0 to 50/50. The weight-average molecular weight of lactic acid/glycolic acid copolymer is preferably about 5,000 to about 30,000, more preferably about 5,000 to 20,000.

Detailed Description Paragraph Right (58):
When hydroxybutyric acid/glycolic acid copolymer (e.g., 2-hydroxybutyric acid/glycolic acid copolymer) is used as the above polymer, the molar ratio of hydroxybutyric acid/glycolic acid is preferably 100/0 to 25/75, more preferably 100/0 to 50/50. In particular, the molar ratio of 2-hydroxybutyric acid/glycolic acid is preferably about 60/40 to about 30/70. The weight-average molecular weight of hydroxybutyric acid/glycolic acid copolymer is preferably about 5,000 to about 25,000, more preferably about 5,000 to about 20,000.

Detailed Description Paragraph Right (59):
When butyric acid/glycolic acid copolymer is used as the above polymer, the molar ratio of butyric acid/glycolic acid is preferably about 100/0 to 25/75.

Detailed Description Paragraph Right (60):
When a mixture of polylactic acid (A) and glycolic acid/2-hydroxybutyric acid copolymer (B) , for example, is used as the above polymer, the mixing

Detailed Description Paragraph Right (63):
The polydispersity of the polymer is defined as the value of weight average molecular weight/number average molecular weight and it should be between 1 and 3.5, preferably between 1.5 and 2.5.

Detailed Description Paragraph Right (64):
The amount of the polymer to be used depends upon the degree of the pharmacological activity, release rate and release period of the physiologically active substance, etc. For example, the polymer is used as the microcapsule base in an amount of about 0.2 to about 10,000 times by weight, preferably about 1 to about 1,000 times by weight, the weight of the physiologically active substance.

Detailed Description Paragraph Right (65):
The concentration of the polymer in the oil phase is selected from the range of about 0.5% to about 90% (W/W), preferably about 2% to about 60% (W/w).

Detailed Description Paragraph Right (66):
In order to inhibit the initial release of the physiologically active substance from the microcapsules, it is advantageous to add basic substances or oils and fats to the solution of a polymer in an organic solvent. The basic substances include, for example, basic amino acids such as L-arginine, N-methylglutamine, L-lysine, etc. In particular, L-arginine or N-methylglucamine is preferred. The oils and fats include, for example, vitamin E, intermediate fatty acids (e.g., miglyols), cholesterol, phospholipids, etc. The concentration of the basic substance in the solution of a polymer in an organic solvent is about 0.01% to about 20% (W/W), preferably about 0.1% to about 5% (W/W), more preferably about 0.1% to about 3% (W/W). The concentration of the oils and fats in the solution of a polymer in an organic solvent is about 0.01% to about 30% (W/W), preferably about 0.1% to about 20% (W/W), more preferably about 0.2% to about 10% (W/W).

Detailed Description Paragraph Right (67):
In the present invention, the aqueous phase preferably also contains an osmotic pressure adjustor. Any osmotic pressure adjustor can be used so long as it produces osmotic pressure in an aqueous solution thereof.

Detailed Description Paragraph Right (75):
Examples of the above water-soluble polysaccharides include glucans such as cellulose, starch, glycogen, etc., galacturonan such as pectic acid, etc., mannuronan such as alginic acid, etc., fructans such as inulin, levan, etc., N-acetylglycosamine polymers such as chitin, etc., xylans such as xylan of rice straw, etc., diheteroglucans such as mannan, glucomannan, galactomannan, hyaluronic acid, chondroitin sulfate, heparin, etc. In particular, glucans, and diheteroglucans are preferred.

Detailed Description Paragraph Right (80):
These osmotic pressure adjustors can be used alone or in combination thereof. When the osmotic pressure adjustor is a non-inonic material, the concentration of the osmotic pressure adjustor in the outer aqueous phase is about 0.001% to about 60% (W/W), preferably about 0.01 to about 40% (W/W), more preferably about 0.05 to about 30% (W/W). When the osmotic pressure adjustor is an ionic material, it is used in a concentration calculated by dividing the above concentration by the total ionic valency. The osmotic pressure adjustor may be added so that their concentration exceeds their solubility, and a part of it may be dispersed.

Detailed Description Paragraph Right (82):
Initially, an amorphous water-soluble physiologically active substance is dispersed in a solution of a polymer in a water-insoluble organic solvent, and the resulting dispersion is mixed well to obtain an s/o type emulsion. In the emulsion, the physiologically active substance is substantially homogeneously dispersed in the polymer solution.

Detailed Description Paragraph Right (83):
If the water-soluble physiologically active substance is available in amorphous form, it can be used as it is. Even if it is available in crystalline form, however, it can be used after making it amorphous. The amorphous water-soluble physiologically active substance is preferably obtained from an aqueous solution, preferably a dilute aqueous solution, of a water-soluble physiologically active substance by a rapid drying process such as freeze drying or spray drying. As described above, the amorphous water-soluble physiologically active substance is preferably used in the form of microparticles, and the average particle size of the physiologically active substance is generally about 1 nm to about 10 .mu.m, preferably about 1 nm to about 1 .mu.m. If the physiologically active substance is available in the form of microparticles, it can be used as it is. If not, it can be used after pulverizing it to microparticles by conventional methods such as the jet mill method, atomization, or ball mill method.

Detailed Description Paragraph Right (84):
The water-insoluble organic solvent is not specifically limited so long as it dissolves the polymer and is insoluble in water. Examples of the water-insoluble organic solvents include halogenated hydrocarbons (e.g., dichloromethane, chloroform, dichlorohexane, chloroethane, dichloroethane, trichloroethane, carbon tetrachloride, etc.), esters (e.g., ethyl acetate, etc.), ethers (e.g., ethyl ether, etc.), aromatic hydrocarbons (e.g., benzene, toluene, etc.), hydrocarbons (e.g., n-pentane, n-hexane, etc.), etc.

Detailed Description Paragraph Right (85):
The emulsification of the above s/o type emulsions can be carried out by conventional dispersion techniques such as intermittent shaking, mixing by means of a mixer (e.g., propeller agitator, turbine agitator, etc.), colloid mill operation, mechanical homogenization, ultrasonication, etc. In this case, it is advantageous to use the above water-insoluble organic solvent in combination with a water-soluble organic solvent. The water-soluble organic solvent is not specifically limited so long as it is soluble in water and miscible with the above water-insoluble organic solvent. Examples of the water-soluble organic solvents include alcohols (e.g., methanol, ethanol, propyl alcohol, isopropyl alcohol, etc.), acetone, acetonitrile, etc. In the s/o type emulsions, it is preferred that the physiologically active substance be dispersed in the form of fine microparticles having an average particle size of about 1 nm to about 10 .mu.m, preferably about 1 nm to about 1 .mu.m.

Detailed Description Paragraph Right (86):
The s/o type emulsion thus prepared is subjected to in-water drying in an aqueous phase. Preferably, the aqueous phase contains an osmotic pressure adjustor in the concentration noted above. That is, the oil phase is added to the second phase (aqueous phase) to form an s/o/w type emulsion, followed by removal of the solvent in the oil phase to prepare microcapsules. The second phase (aqueous phase) may contain an emulsifying agent. Any emulsifying agent can be used so long as it generally forms stable o/w type emulsions. Examples thereof include anionic surfactants (e.g., sodium oleate, sodium stearate, sodium laurate, etc.); nonionic surfactants such as polyoxyethylenesorbitan fatty acid esters (e.g., TWEEN 60, TWEEN 80 (Atlas Powder

Co.), etc.), polyoxyethylene castor oil derivatives (e.g., HCO-60, HCO-50 (Nikko Chemicals), etc.), polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethyl cellulose, lecithin, gelatin, etc. These emulsifying agents can be used alone or in combination thereof. They are used in a concentration appropriately selected from the range of about 0.01% to about 20% (W/W), preferably about 0.05% to about 10% (W/W).

Detailed Description Paragraph Right (87):
The solvent in the oil phase can be removed by conventional methods, for example, by stirring the emulsion with a propeller-type stirrer, magnetic stirrer, etc., under atmospheric pressure or gradually reduced pressure, or by evaporating the solvent while controlling the degree of vacuum by using a rotary evaporator, etc. In this case, when solidification of the polymer proceeds to some degree and the loss of the physiologically active substance caused by its release from the internal phase is decreased, the s/o/w type emulsion may be warmed gradually to remove the solvent completely. This operation shortens the removal time. Alternatively, when the polymer is thickened and solidified by methods other than those based on temperature, the solvent may be removed by merely allowing the s/o/w type emulsion to stand with stirring, or by warming the emulsion, or by spraying nitrogen gas, etc. This step of removing the solvent is important and greatly influences the surface structure of microcapsules that controls the release of the physiologically active substance. For example, rapid removal of the solvent produces many or larger pores on the surface, thereby increasing the release rate of the physiologically active substance.

Detailed Description Paragraph Right (97):
aqueous solid suppositories, semi-solid or liquid suppositories by per se known methods. The oleaginous bases for the above composition are not specifically limited so long as they do not dissolve the microcapsules. Examples thereof include higher fatty acid glycerides [e.g., cacao butter, Witepsol (Dynamit-Nobel, Germany), etc.], intermediate fatty acids [e.g., Miglyol (Dynamit-Nobel), etc.], vegetable oils (e.g., sesame oil, soybean oil, cottonseed oil, etc.), etc. The aqueous bases include, for example, polyethylene glycol and propylene glycol. The aqueous gels include, for example, natural gum, cellulose derivatives, vinyl polymers, polyacrylates, etc.

Detailed Description Paragraph Right (100):
Thus, pharmaceutical compositions can be prepared as the microcapsules which comprises a physiologically active substance in an effective therapeutic amount that is larger than a conventional unit dose and a biocompatible polymer and which can achieve sustained-release of the physiologically active substance over a long period.

Detailed Description Paragraph Right (106):
The anti-platelet aggregation agent (S)-4-[(4-amidinobenzoyl)glycyl]-3-methoxy-carbonylmethyl-2-oxopiperazine- 1-acetic acid (abbreviated herein as Compound A) in amorphous form (450 mg) obtained by freeze drying was dispersed in a solution of lactic acid/glycolic acid copolymer (lactic acid/glycolic acid=75/25, average molecular weight calculated as polystyrene=10500) (4.05 g) in dichloromethane (4 ml). The drug in the dispersion was pulverized to microparticles using Polytron, a homogenizer manufactured by Kinematica, Switzerland. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% aqueous PVA (polyvinyl alcohol) solution (800 ml) containing 2.7 (w/v)% sodium chloride. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized from the microcapsules and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (107):
Compound A in crystalline form (450 mg) was dispersed in the above solution of lactic acid/glycolic acid copolymer (4.05 g) in dichloromethane (4 ml), the drug in the dispersion having been pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% PVA aqueous solution (800 ml) containing 2.7 (w/v)% sodium chloride. Thus, powdery microcapsules were obtained in the same manner as that described above.

Detailed Description Paragraph Right (109):
Compound A in amorphous form (450 mg) obtained by freeze drying was dispersed in a

solution of lactic acid/glycolic acid copolymer (lactic acid/glycolic acid=75/25, average molecular weight calculated as polystyrene=10500)(3.96 g) in dichloromethane (4 ml) in which L-arginine (90 mg) had been dissolved. The drug in the dispersion was pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% aqueous PVA solution (800 ml) containing 2.7 (w/v)% sodium chloride. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized from the microcapsules and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (111):
Compound A in amorphous form (450 mg) obtained by freeze drying was dispersed in a solution of lactic acid/glycolic acid copolymer (lactic acid/glycolic acid=75/25, average molecular weight calculated as polystyrene=8400)(3.96 g) in dichloromethane (4 ml) in which L-arginine (90 mg) had been dissolved. The drug in the dispersion was pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% PVA aqueous solution (800 ml) containing 2.7 (w/v)% sodium chloride. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized from the microcapsules and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (113):
Compound A in amorphous form (150 mg) obtained by spray drying was dispersed in a solution of lactic acid/glycolic acid copolymer (lactic acid/glycolic acid=50/50, average molecular weight calculated as polystyrene=8000)(4.26 g) in dichloromethane (4 ml) in which L-arginine (90 mg) had been dissolved. The drug in the dispersion was pulverized to microparticles using Polytron. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% PVA aqueous solution (800 ml) containing 0.9 (w/v)% sodium chloride. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized from the microcapsules and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried together with mannitol for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (114):
Freeze-dried Compound A (300 mg) was dispersed in a solution of hydroxybutyric acid/glycolic acid copolymer (hydroxybutyric acid/glycolic acid=50/50, average molecular weight calculated as polystyrene=12000)(4.2 g) in dichloromethane (4 ml). The drug in the dispersion was pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% PVA aqueous solution (1000 ml) containing 1.8 (w/v)% sodium chloride. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized from the microcapsules and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried together with mannitol for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (120):
The GPIIb/IIIa antagonist (Arg-Gly-Asp-Ser)tetramer in amorphous form (200 mg) obtained by freeze drying was dispersed in a solution of lactic acid/glycolic acid copolymer (lactic acid/glycolic acid=90/10, average molecular weight calculated as polystyrene=12000)(3.7 g) in dichloromethane (4 ml) in which L-arginine (100 mg) had been dissolved. The drug in the dispersion was pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.5 (w/v)% PVA aqueous solution (800 ml) containing 2.7 (w/v)% sodium chloride cooled to 15.degree. C. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried together with mannitol for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (121):

The antibiotic cefoxitin sodium in amorphous form (150 mg) obtained by freeze drying was dispersed in a solution of hydroxybutyric acid/glycolic acid copolymer (hydroxybutyric acid/glycolic acid=75/25, average molecular weight calculated as polystyrene=14000) (4.7 g) in dichloromethane (4 ml) in which N-methylglucamine (150 mg) had been dissolved. The drug in the dispersion was pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.2 (w/v)% PVA aqueous solution (800 ml) containing 15 (w/v)% mannitol cooled to 15.degree. C. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried together with mannitol for a day to obtain powdery microcapsules.

Detailed Description Paragraph Right (122):
The bone resorption inhibitor 4-phenoxybutylaminomethylene-1,1-bisphosphonate disodium salt in amorphous form (200 mg) obtained by freeze drying was dispersed in a solution of lactic acid/glycolic acid copolymer (lactic acid/glycolic acid=90/10, average molecular weight calculated as polystyrene=8400) (3.7 g) in dichloromethane (4-ml) in which L-arginine (100 mg) had been dissolved. The drug in the dispersion was pulverized to microparticles using Polytron homogenizer. Then, s/o/w type emulsions were prepared using a homogenizer in 0.1 (w/v)% PVA aqueous solution (800 ml) containing 10 (w/v)% mannitol cooled to 15.degree. C. Then, the emulsions were slowly stirred with a conventional propeller agitator for 3 hours. After dichloromethane vaporized and the microcapsules hardened, the microcapsules were collected by centrifugation and at the same time washed with purified water. The collected microcapsules were freeze-dried for a day to obtain powdery microcapsules.

CLAIMS:

1. A sustained-release microcapsule which is obtained by the steps comprising:

selecting a dispersion of an amorphous water-soluble pharmaceutical agent having a particle size of from 1 nm-10 .mu.m in a solution of a polymer in an organic solvent, wherein said pharmaceutical agent is dispersed in an amount of from 0.001-90% (w/w) and said polymer has a wt. avg. molecular weight of from 2,000-800,000;

dispersing said dispersion of amorphous water-soluble pharmaceutical agent in an aqueous phase to prepare an s/o/w emulsion; and

subjecting the s/o/w emulsion to in-water drying.

2. The microcapsule according to claim 1, wherein the concentration of the pharmaceutical agent in the solution of a polymer in an organic solvent is from about 0.01% to about 70% (W/W).

3. The microcapsule according to claim 1, wherein the solution of a polymer in an organic solvent additionally contains a basic substance.

7. The microcapsule according to claim 3, wherein the concentration of the basic substance in the solution of a polymer in an organic solvent is about 0.1% to about 3% (W/W).

11. The microcapsule according to claim 1, wherein the pharmaceutical agent is dispersed in the polymer.

12. The microcapsule according to claim 1, wherein the amorphous water-soluble pharmaceutical agent is obtained from an aqueous solution of a water-soluble pharmaceutical agent by a drying process.

15. The microcapsule according to claim 1, wherein the water-solubility of the pharmaceutical agent is not less than about 1 g/100 ml at 20.degree. C.

16. The microcapsule according to claim 1, wherein the water-solubility of the pharmaceutical agent is not less than about 5 g/100 ml at 20.degree. C.

17. The microcapsule according to claim 1, wherein the average particle size of the pharmaceutical agent is not more than about 1 .mu.m.

29. The microcapsule according to claim 1, wherein the polymer is a biodegradable polymer.

30. The microcapsule according to claim 29, wherein the biodegradable polymer is a polyester.